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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/607,623	06/27/2003	Haim D. Danenberg	92114.005US1	7907

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EXAMINER	
JAGOE, DONNA A	

ART UNIT	PAPER NUMBER
1619	

NOTIFICATION DATE	DELIVERY MODE
02/04/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/607,623	DANENBERG ET AL.	
	Examiner	Art Unit	
	Donna Jagoe	1619	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 November 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-10,16,17,19,20,23-26,31-35,39-41,71 and 72* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-10,16,17,19,20,23-26,31-35,39-41,71 and 72* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *See Continuation Sheet*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :11/10/09, 11/10/09, 12/22/09 & 12/22/09.

DETAILED ACTION

Claims 1, 4-10, 16, 17, 19, 20, 23-26, 31-35, 39-41, 71 and 72 are pending in this application.

Applicants' arguments filed November 10, 2009 have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 4-10, 16, 17, 19, 20, 23-26, 31-35, 39-41, 71 and 72 rejected under 35 U.S.C. 103(a) as being unpatentable over Pennanen et al. (U) and Hack et al. U.S. Patent No. 6,090,777 in view of Ylitalo, Gen. Pharmacology. 2002 and Hope et al. U.S. Patent No. 6,139,871 A.

Pennanen et al. teach that when bisphosphonates are encapsulated in liposomes, the inhibitory potency against proinflammatory cytokines (IL-1β, IL-6 and TNF-α) is enhanced by a factor of 10-20. The complex formation of bisphosphonates with extracellular calcium enhanced the **uptake** of the compounds (uptake is also known as phagocytosis)(see abstract). The inhibition of inflammatory cytokine production and secretion **by macrophages** is a valuable marker for potential anti-inflammatory drugs (page 916, column 2). Liposome encapsulated clodronate was over ten times more potent inhibitor of cytokine secretion from RAW264 cells than free drug and the inhibitory potency of etidronate was also considerably increased (page 917, column 2).

It does not teach treatment of a patient having a myocardial infarction (MI).

Hack et al. teach that the inflammatory reaction which occurs in the course of an acute myocardial infarction (AMI) comprises some important events: including the production of cytokines such and tumor necrosis factor α (TNF-α) and interleukin-6 and activation of complement (column 1, lines 56-63) and inhibition of this complement would reduce or prevent myocardial damage (zone of infarct) (column 5, lines 6-18). It would have been made obvious to one of ordinary skill in art at the time it was made to administer the liposome encapsulated bisphosphonates of Pennanen et al. motivated by the teaching that the inhibitory potency against proinflammatory cytokines (IL-1β, IL-6 and TNF-α) is enhanced by a factor of 10-20 when bisphosphonates are encapsulated in liposomes and further motivated by the teaching of Hack et al. who teach that the zone of infarct can be reduced by inhibiting the activation of complement (paragraph 5, lines 6-18), by administration of an agent that has anti-inflammatory properties and is a cytokine antagonist (claims 19 and 21) (Pennanen et al. teaches that bisphosphonates are anti-inflammatory agents that inhibit cytokine production and secretion).

Ylitalo teaches liposomal (encapsulated) formulations of bisphosphonates such as clodronate and etidronate (page 293, column 2, paragraph 3), and teach that bisphosphonates inhibit atherosclerosis (page 287, column 1 to page 288, column 2). Ylitalo teaches that bisphosphonates anti-atherogenic effect is due to a direct effect on arterial wall wherein the bisphosphonates interact with the subendothelial lipid phagocyting cells (intracellular inhibitor)(page 292, column 1, paragraph 1) and macrophages are especially sensitive to bisphosphonates, and bisphosphonates

suppress macrophages and exert cytotoxicity and suppress the appearance of macrophages in arterial wall during atherogenesis. Ylitalo does not teach depletion of macrophages, however, it teaches that the appearance of macrophages is suppressed. Since the term "depletion" is synonymous with the term "eliminating all macrophages" and both circumscribe methods of treatment having absolute success. Absolute success is not reasonably possible with most diseases, especially ones having etiologies as complex as atherosclerosis and AMI.

Pennanen et al., Hack et al. and Ylitalo et al. do not teach the size of the liposomes.

Hope et al. teach liposomes of 0.1 to 0.15 microns for treatment of atherosclerosis (see abstract). It would have been made obvious to one of ordinary skill in art at the time it was made to treat AMI in a patient by administering encapsulated bisphosphonates in liposomes in a size of 0.1 to 1 micron motivated by the teaching of Pennanen et al. who teach that liposomal bisphosphonates are 10-20 times more potent in inhibiting proinflammatory cytokines and the teaching of Hack et al. who teach that by inhibiting proinflammatory cytokines, formation of complement is inhibited and thus the zone of infarction is reduced. Regarding the size of the liposome, instant claims 1, 25 and 71 is drawn to a formulation with a size range of 0.03-1 micron. Hope et al. teach a liposome formulation in a range of from 0.1 to 0.15 microns. This amount overlaps and encompasses the claimed size. A *prima facie* case of obviousness exists where the claimed ranges are close enough that one skilled in the art would have expected them to have the same properties.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 4-10, 16, 17, 19, 20, 23-26, 31-35, 39-41, 71 and 72 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-12 of copending Application No. 10/871488.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant and conflicting claims recite substantially the same subject matter, differing only in the description of the particular components claimed. For instance, conflicting claim 1 requires the method of treating an acute coronary syndrome with is inclusive of an acute myocardial infarction of the instant claims. It would have been obvious to anyone of ordinary skill in the art that the claims

overlapped in scope in this manner. One skilled in the art would have been motivated to have interpreted the claims as broadly as is reasonable, and in doing so recognize that they are coextensive in scope and thus the proper subject of an obviousness-type double patenting rejection as outlined by *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1, 4-10, 16, 17, 19, 20, 23-26, 31-35, 39-41, 71 and 72 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 4-10, 17-20, 23, 24, 27-29, 32-36, 38 and 41 of copending Application No. 11/190787. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant and conflicting claims recite substantially the same subject matter, differing only in the description of the particular components claimed. For instance, conflicting claim 1 requires the method of treating an ischemia-reperfusion injury with is inclusive of the acute myocardial infarction of the instant claims as indicated in conflicting claim 23. It would have been obvious to anyone of ordinary skill in the art that the claims overlapped in scope in this manner. One skilled in the art would have been motivated to have interpreted the claims as broadly as is reasonable, and in doing so recognize that they are coextensive in scope and thus the proper subject of an obviousness-type double patenting rejection as outlined by *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Thus the claims fail to patentably distinguish over the state of the art as represented by the cited references.

Accordingly, for the above reasons, the claims are deemed properly rejected and none are allowed.

Response to Arguments

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., the treatment of a myocardial infarction during an acute MI) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). The claims are drawn to a subject "having" an acute myocardial infarction (instant claim 1),"having an acute myocardial infarction followed by myocardial necrosis" (instant claim 25), "during or as early as possible" after an acute myocardial infarction" (instant claim 40) and "having an acute myocardial infarction followed by myocardial necrosis" (instant claim 71). None of these claims are drawn to treatment of a patient during an acute myocardial infarction (with the exception of instant claim 40 although the claim has an alternative to treat "as early as possible after the AMI). The word "having" in instant claims 1, 25 and 71 denotes that the patient is in possession of a myocardial infarction, but does not specifically

convey that the treatment is during the myocardial infarction. Applicant refers to the Szebeni reference wherein it is stated that 'liposomes are recognized by the complement system as foreign and they trigger C activation. Applicant appears to be using the reference to discredit the Hack reference that teaches treatment of AMI by inhibition of the complement system. In response, the liposomes of Szebeni are haptenized liposomes. Haptenes are small molecules which can elicit an immune response only when attached to a large carrier, such as a liposome. Thus it is not unexpected that these haptenized liposomes of Szebeni activated complement. However, they are not bisphosphonates that are encapsulated in liposomes as in Pennanen et al. nor are they the same as the liposomes instantly claimed.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Applicant states that Pennanen Ylitalo and Hope references describe treatments for chronic diseases, however, none of the instant claims specifically recite emergency treatment of a patient during an acute myocardial infarction as noted supra.

Applicant states that the obviousness type double patenting rejections are premature and request reconsideration and withdrawal. In response, the rejections are maintained and hereby repeated.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Donna Jagoe whose telephone number is (571) 272-0576. The examiner can normally be reached on Monday through Friday from 8:00 A.M. - 4:30 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne (Bonnie) Eyler can be reached on (571) 272-0871. The fax phone

number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/YVONNE L. EYLER/
Supervisory Patent Examiner, Art Unit 1619

Donna Jagoe /D. J./
Examiner
Art Unit 1619

January 19, 2010